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Real-world treatment patterns among French patients with metastatic castration-resistant prostate cancer under abiraterone or enzalutamide.

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Abstract (250/250 words)

Purpose. Using large French retrospective study cohort of chemotherapy-naïve metastatic castration-resistant prostate cancer patients (mCRPC; n = 10,308) comparing survival between patients who initiated abiraterone (ABI; 64%) and those initiating enzalutamide (ENZ; 36%), the present objective was to describe treatment patterns in the two years following initiation.

Method. Using the national health data system (SNDS) from 2014 to 2018, we first explored the number of treatment lines, and secondly, patterns of patient management using state sequence analysis; cluster analyses were performed on the 0-12 month and 13-24 month periods. Age, Charlson score, and duration of androgen deprivation therapy (ADT) were obtained for each cluster in the 1st year of follow-up.

Results. Patients with only one treatment line accounted for 52%. In the 0-12 month sequence analysis, the main clusters among ABI/ENZ new users involved patients who continued the initial treatment (54%/65% respectively) and discontinued active treatment (14.5% for both). Less than 2 years exposure to ADT prior to ABI/ENZ initiation was frequently observed for non-controlled mCRPC, as shown in the death and switch from ABI/ENZ to docetaxel clusters. The clusters for a switch ABI/ENZ to ENZ/ABI involved 6-11% of the patients.

Conclusion. Our study suggested fairly similar patterns between ABI and ENZ initiation. The cluster of patients with active treatment discontinuation needs to be further investigated, as well as factors influencing therapeutic choice. Better understanding for the use of second-generation hormone therapy in mCRPC in real life, could improve its implementation by clinicians in the early stages of prostate cancer.

Introduction

In the 2010s, the arrival of two androgen receptor-targeted agents (ARTAs), abiraterone (ABI) and enzalutamide (ENZ), profoundly modified the management of metastatic castration-resistant prostate cancer (mCRPC), where docetaxel was previously the standard care. Since then, much has been written about the optimal sequence of treatment, and authors have highlighted cross-resistance between ARTAs when used sequentially¹⁻³. The recent use of ARTAs in the early stages of prostate cancer and the arrival of drugs belonging to other pharmacological classes have further complicated the debate³.

Recently, in a direct comparison of ARTAs in a French national cohort (the 'SPEAR' study, Safety and Performance of Enzalutamide and Abiraterone) from 2014 to 2018, treatment with ENZ was found to significantly improve overall survival among men with mCRPC in comparison with those who received ABI (HR 0.90, 95% CI: 0.85,0.96; median OS, 31.7 months for ABI and 34.2 months for ENZ)⁴. This is consistent with another analyses using the US Veteran Health Administration database^{5,6}. To go beyond this intent-to-treat analysis, the objective of our present analysis using the SPEAR study was to describe the treatment patterns in the two years after ARTA initiation.

Material and methods

Study design and population

The SPEAR study is a French population-based cohort study, the design of which has been described previously⁴. We used the pseudo-anonymous French national health data system (Système National des Données de Santé, SNDS), which covers about 99% of the French population. The SNDS contains exhaustive individual data on reimbursements linking data from health ambulatory services (medical consultation, imagery, biological acts, and drug

prescriptions) to the hospital discharge database (diagnoses using the International Statistical Classification of Diseases, 10th revision [ICD-10] codes, medical acts, and certain costly drugs); it also contains demographic data and vital status. The SNDS does not provide any clinical information.

Aligning on certain features of randomized trials, the SPEAR study method was based on the principles of an emulated target trial⁷. Eligible men were patients with a first reimbursement of ABI or ENZ in 2014-2017, without records of ARTA reimbursements in the 3 previous years (used as a proxy for progression toward the mCRPC stage), and followed through to 2018. Over this study period, the only ARTA indication was mCRPC. The exposure groups were based on the first drug received (ABI or ENZ) and this initiation was considered as the start of the follow-up (Time 0). Patients were to be free from cancers other than prostate cancer and were to have had no chemotherapy for prostate cancer prior to Time 0, going back as far as 2009. Overall, the SPEAR cohort included 10,308 new users, 64% were treated with ABI (n = 6 585) and 36% with ENZ (n = 3 723). The baseline characteristics have been previously described⁴.

Analysis

The first step was an overall description of the number of treatment lines from the first ABI or ENZ use up to death or the end of follow-up (administrative censoring December 31st, 2018), drawing on the previously used dataset⁴. We noted the proportion of patients who switched from ARTA to another active treatment (ABI, ENZ, chemotherapy) per quarter in the first year of follow-up. The median duration of treatment lines was not extracted because it would have needed to take censoring into account. Furthermore, durations are difficult to interpret, as they depend on the type of treatment used (ARTA, chemotherapy) and on parameters outside

our control on account of the lack of clinical information (prescriber's intentions, patient's condition, response and tolerance to treatment).

In a second step, we further explored patient management sequences, year by year, providing a description of the duration and type of management in the 2 years following initiation of ABI or ENZ. Taking into account the chronology of drug reimbursements, state sequence analysis (SSA) was used to identify specific treatment patterns in the study population. This methodology has previously been used to analyse care trajectories among French multiple sclerosis patients⁸. Different "states" for the patients were identified here: treated with ABI, ENZ, docetaxel or cabazitaxel chemotherapy, discontinuation of treatment (ABI, ENZ, chemotherapy), death and end of follow-up.

The general principle of SSA is to compare sequences for the succession of states. The term "sequence" refers to the entire individual therapeutic trajectory.

We used the month as the time unit in the sequence and data was managed to assign one of the states for each patient to each month. When different states could be assigned to the same month, the last state occurring was considered. Using SSA methodology as previously described⁹, after extracting individual therapeutic sequences, a two-by-two comparison of sequences was performed using the optimal matching (OM) method to measure dissimilarities between sequences¹⁰. The matrix of substitution costs was estimated empirically using the transition rates observed in the dataset. The dissimilarity matrix was used to cluster sequences and to create a typology of homogeneous patterns of treatment with an agglomerative hierarchical clustering method using the Ward criterion¹⁰. The optimal number of clusters was chosen on the basis of the fall in inertia. By construction, "early" and "late" clusters were in some cases distinguished: "early" refers to patients whose change in

status occurred before 6 months of follow-up, and "late" to patients for whom the change occurred between 6 and 12 months of follow-up.

A first cluster analysis was performed on the 0-12 month period to identify groups of similar patterns for the initial use of ABI or ENZ. Then, based on the 0-12 month clusters identified, a second clustering was performed for the 13-24 month period to identify subsequent clusters. Only patients still alive at 12 months were included in the 13-24 month analysis. All patients had the same sequence length of 12 months, except for right-truncated sequences (end of follow-up or death). These grouped sequences are presented visually on an index plot.

For each cluster in the 0-12 month period, we described the nature of the first state change, the median duration to the first change, median age, Charlson score, and duration of androgen deprivation therapy (ADT). Multiple testing (pair-wise), to compare age and ADT duration across clusters, was implemented with permutation-style-adjusted p-values; the corrected statistical threshold was set at 0.05. To take account of deaths during the first year of follow-up in each cluster, subsequent clustering over the 13-24 month period was described only in clusters of >100 patients alive at 12 months, and only large clusters (>30%) are shown for ease of reading.

Analyses were performed with R v3.6.1 software. The sequence analysis and the clustering used the TraMineR library 2.2-0.1¹¹ and the WeightedCluster library v1.4¹².

Results

Overall description

On the basis of available follow-up, whatever the first ARTA used among the 10,308 new users, 52.2% of patients received 1 line of treatment, followed by 24,8 %, 12.1 % and 10.9 % who had 2, 3 and ≥ 4 lines respectively. [Figure 1](#) shows the number of lines of treatment since the initiation of each ARTA. It can be noted that 0.5 % of the patients switched directly from ARTAs to cabazitaxel. The first switch to another treatment occurred for approximately 25-30% of patients at 3-6, 6-9 and 9-12 months ([Supplemental eTable 1](#)).

0-12 month and 13-24 month sequences

Within the first year of follow-up, the therapeutic sequences among ABI and ENZ new users led respectively to a seven- and eight-cluster pattern ([Figure 2](#), [Figure 3](#)). The main cluster identified in both groups involved patients who continued the initiation drug over the year of the initiation of treatment (about 54% and 65%, respectively). The following two representative clusters identified were patients who stopped active treatments (about 14.5 % in both groups, grouping 'early' and 'late' clusters with the same pattern in the ENZ group) and patients who died prematurely (about 10% in both groups). Switches to another ARTA or docetaxel chemotherapy was observed in less than 11.5% of cases (grouping 'early' and 'late' clusters with the same pattern) in both groups. The time to the first state change and the nature of the subsequent treatments are described in [Supplemental eTable 2](#) and [eTable 3](#).

The characteristics of each cluster are presented in [Table 1](#) and [Table 2](#). The oldest mean ages (> 80 years) were observed in both groups for patients who died or switched to another ARTA, as well as for the "discontinuation of active treatment" cluster in the ENZ group ($p < 0.05$; [Supplemental eTable 4-5](#)). For both groups, patients who switched from ARTA to docetaxel

were on average the younger ones (about 73-74 years) with the largest proportion of patients with less than 2 years of ADT history compared to most other groups ($p < 0.05$; Supplemental eTable 4-5). In the cluster of patients who continued ABI, we observed a larger proportion of patients with > 3 years of ADT history compared to all other groups ($p < 0.05$; Supplemental eTable 4-5).

The main sequences observed in the second year of treatment are presented in Figure 2 and Figure 3. Among patients who continued the initiation ARTA in the first year, 44% and 56% respectively continued their ARTA in the second year. By construction, for most other clusters in the 0-12 month period, a cluster grouping patients with administrative censure or death ('End of follow-up or death') appeared frequently (35-50% of patients) in the 13-24 period. Some clusters contain heterogeneous sequences, especially in clusters with small numbers of patients. Details of the clusters of patients who discontinued active treatment in the first year are provided over the 13 to 24 month period in the Supplemental (eFigure 1 for ABI; eFigure 2 and 3 for ENZ): approximately 12.5% to 22% had a resumption of ARTA; most of the remainder did not resume any treatment or had no observable follow-up and/or died.

Discussion

Using a French national cohort of 10,308 new users of ARTAs in 2014-2017, with a median follow-up of 20-23 months, we observed that 52% of patients had only one line of treatment. More precisely, the sequence analysis suggests that 54-65% of new ABI/ENZ users continued the initiated treatment over the first 12 months (main cluster), and about half of them also continued it in the second year of treatment. This suggests that for a significant proportion of patients, prostate cancer appears as a less aggressive cancer, consistent with a large proportion of patients with > 3 years of ADT, appearing to respond to ARTAs, and with a good tolerance to treatment.

Surprisingly, a cluster of patients who stopped all active treatment (most of them remaining alive) was observed for about 14.5% of ARTA new users. Among them, 37-49% discontinued active treatment, most of them remaining alive in the second year of follow-up. It can be noted that the end of the follow-up in the second year truncated the sequences to the right, which could have an impact on the overall understanding of this cluster of patients with similar patterns. In the second year of follow-up, some patients resumed active treatment (ABI/ENZ rechallenge, ARTA switch or docetaxel use), which could suggest, in accordance with literature, that discontinuation of active treatment could be a more or less transient pause (no additional information on the median time spent without active treatment) as a result of adverse drug reactions or poor efficacy¹³⁻¹⁵. Overall, the patients were elderly, (mean age 78-81 year); up to 25% of them had a ≥ 3 Charlson score ≥ 3 , and about 40% had less than 2 years and 40% more than 3 years of ADT. In a Swedish population-based study, the authors identified predictors of drug discontinuation, including, as expected, a short period on ADT before ARTA initiation (≤ 1 year), age > 75 year and Charlson index ≥ 3 ¹⁶. A specific analysis of this cluster of patients taking into account access to care (specialist consultation,

hospitalization...) could be interesting, in particular to estimate whether adverse drug reactions could be suspected or whether palliative care was planned.

Besides this, and as expected, death was observed in the first year of treatment for about 10% of the patients, mainly under first-line ARTA treatment. This could be explained by unfavorable demographic characteristics (mean age 82 years; Charlson score ≥ 3 for approximately 30% of the patients), as well as by non-controlled disease. This is consistent with the fact that approximately half of these patients had received less than 2 years of ADT before ARTA initiation. Along the same lines, non-controlled disease could be involved for patients who switched from ARTA to docetaxel (9.2% and 4.5% of ABI and ENZ new users respectively), as more than half of the patients had less than 2 year of ADT. This is in agreement with a French study showing that a short time to castration resistance (< 12 months) is associated with poorer efficacy of ARTAs among men with mCRPC, reflecting a more aggressive component of the tumour¹⁷. Concerning drug switches, over the 2014-2018 period, the guidelines of European and French Association of Urology on prostate cancer^{18,19} agreed on the existence of cross-resistance between ARTAs and discouraged the sequential use of ARTAs, preferring docetaxel as a second-line therapy. In our study, about 11% switched from ABI to ENZ and 6% vice versa. This could be related to the lack of available information (especially before 2015) or the lack of broad information to clinicians when data on cross-resistance emerged. Poor health status making patients ineligible for chemotherapy cannot be excluded either. As expected, age and comorbidities also seem to influence the choice of therapy: the switch from ARTA to docetaxel occurred among the "younger" patients (mean age 73-74 years), with a Charlson score ≤ 2 for more than 80%. This is consistent with results from a US Veteran cohort, suggesting that older patients or those with comorbidities were more likely to receive oral therapies that are less toxic than docetaxel²⁰.

The sequence heterogeneity observed in our study after two lines of treatment is evidence of the need for a benefit/risk balance evaluation, taking into account patient comorbidities, potential or known adverse drug reactions, disease progression (speed and existence of molecular alterations in the tumour) and therapeutic options^{3,19,21}. The reasons for drug switches were not known in our study. Given the respective safety profiles of ABI and ENZ, including cardiac disorders or cognitive disorders^{14,22,23}, the occurrence of adverse drug reactions among patients with comorbidities cannot be excluded and could be a factor for definitive discontinuation.

Given the European guidelines on prostate cancer, and considering in particular biological and clinical data on prostate cancer, the therapeutic choice of the first and second lines of treatment for mCRPC seems to entail little ambiguity as to which pharmacological class to choose (ARTA, chemotherapy)¹⁸. However only scarce information is available on patient comorbidities and potential adverse drug reactions that could influence the clinician's therapeutic choice. The 2020 update mentioned a multidisciplinary approach to manage the disease, especially among elderly men²⁴. On the other hand, although international oncology guidelines recommend geriatric assessment²⁵⁻²⁷, online surveys of US oncologists have shown that 60% did not use a geriatric assessment for any of their patients to guide the treatment decision, while 13% used it for all of their geriatric patients; ECOG functional status and history and physician examination were more widely favored. The main reasons cited were the cumbersome nature of the procedure and its lack of value compared to patient history and physical examination²⁸. Recently, using the US Veteran Health Administration database, authors showed a better overall survival and a longer treatment duration with ENZ compared to ABI in veterans over 75 years of age, with cardiovascular disease or diabetes⁶.

In their respective clinical trials, ABI and ENZ have demonstrated oncological benefit only in ECOG 0-1^{29,30}. In real life, our study showed that clinicians did not hesitate to treat patients, even very old patients with comorbidities (> 90 % of patients had a Charlson score ≥ 2) and who were symptomatic and experiencing pain⁴. With a population that is more representative of the target population than that of clinical trials, our results could better inform clinicians in their choice of treatment, particularly for more frail patients. The literature on treatment regimens used in real-life mCRPC patients has expanded in recent years, but has provided little or no information on patient comorbidities or functional status³¹⁻³⁵, suggesting that prostate cancer management and treatment choices remain primarily a matter of oncological outcome. Among the limitations of this study, we have described patterns of treatment among patients who had no contraindications to ABI or ENZ. Thus, this does not describe the patterns for all patients treated with ABI or ENZ. But using an ambivalence approach (in the emulated target trial), we described the treatment patterns of patients liable to switch from one ARTA to another. Our study had no information on clinical and biological data and imagery (including no information on the type and proportion of metastases), which limits our interpretation regarding disease activity, patients' functional status and adverse drug reactions. Hospitalisation for adverse events that could be related to ARTA use has been previously assessed²². We did not study the care consumption (including in relation to prostate cancer disease burden) nor determine whether geriatricians were involved in the overall patient care (using consultations with a geriatrician or a hospital stay in a geriatric department) because it is an ancillary study to the SPEAR study where the primary endpoint was overall survival. But using the SNDS, a comprehensive database, we identified prostate cancer treatments as well as comorbidities from hospital diagnosis codes, chronic disease codes, and drug reimbursements. This information can be used as a proxy for patient frailty. Finally, we have

described the treatment patterns in the first two years of treatment. Given a median overall survival of 32 to 34 months⁴, a descriptive analysis including a third year could shed more light on some sequences.

Conclusion

The analysis of treatment sequences in a French cohort of 10,308 new users of ARTAs over the 2014-2018 period highlights several clusters of treatment patterns in the first two years of follow-up, with apparently similar patterns between ABI and ENZ initiators. The cluster of patients who discontinued their treatment needs to be further investigated. Globally, the impact of patient comorbidities and functional status on therapeutic choice, and the comparison of sequences in terms of oncological outcomes need further investigation. More knowledge on the use of second-generation hormone therapy in mCRPC in real life could improve its use by clinicians in non-metastatic CRPC or in hormone-sensitive prostate cancer, since this is now the standard care.

1) Author contributions

Dr Scailteux, Pr Oger, Ms Kerbrat had full access to all of the data that was used to generate the study population. The database extracted was stored in a dedicated space on the CNAMTS portal. Ms. Kerbrat carried out the data management (cleaning, table design and choice of variables for statistical analyses). They take responsibility for the integrity of the data and the accuracy of the data analysis.

Conception and design: Scailteux, Oger.

Acquisition, analysis and interpretation of the data: All authors.

Drafting of the manuscript: Scailteux.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Kerbrat, Scailteux.

Obtained funding: Scailteux, Oger.

Administrative, technical, or material support: Oger.

Supervision: Oger.

Critique of completed data analysis and interpretation in the manuscript: all authors.

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3) Ethics statement

We used the French National Agency for the Safety of Medicines and Health Products permanent access to French health databases which is automatically granted to certain government agencies, public institutions and public service authorities, and did not require patient consent or ethics committee approval.

4) Conflict of interest

LMS, FB, SK, EO: none.

Sébastien Vincendeau and Romain Mathieu report consulting or advisory roles for Astellas Pharma and Janssen.

Gwenaëlle Gravis advisory/consultancy/speaker bureau for Astellas Pharma, Janssen, Astra Zeneca, AAA (recipient Institution).

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Figure Legend

Figure 1. Number of lines of treatment since initiation of abiraterone or enzalutamide.

Figure 2. Index plot for therapeutic sequences for abiraterone users in the two years following treatment initiation (n = 6585).

Figure 3. Index plot of therapeutic sequences for enzalutamide users in the two years following treatment initiation (n = 3723).

Figure 1.

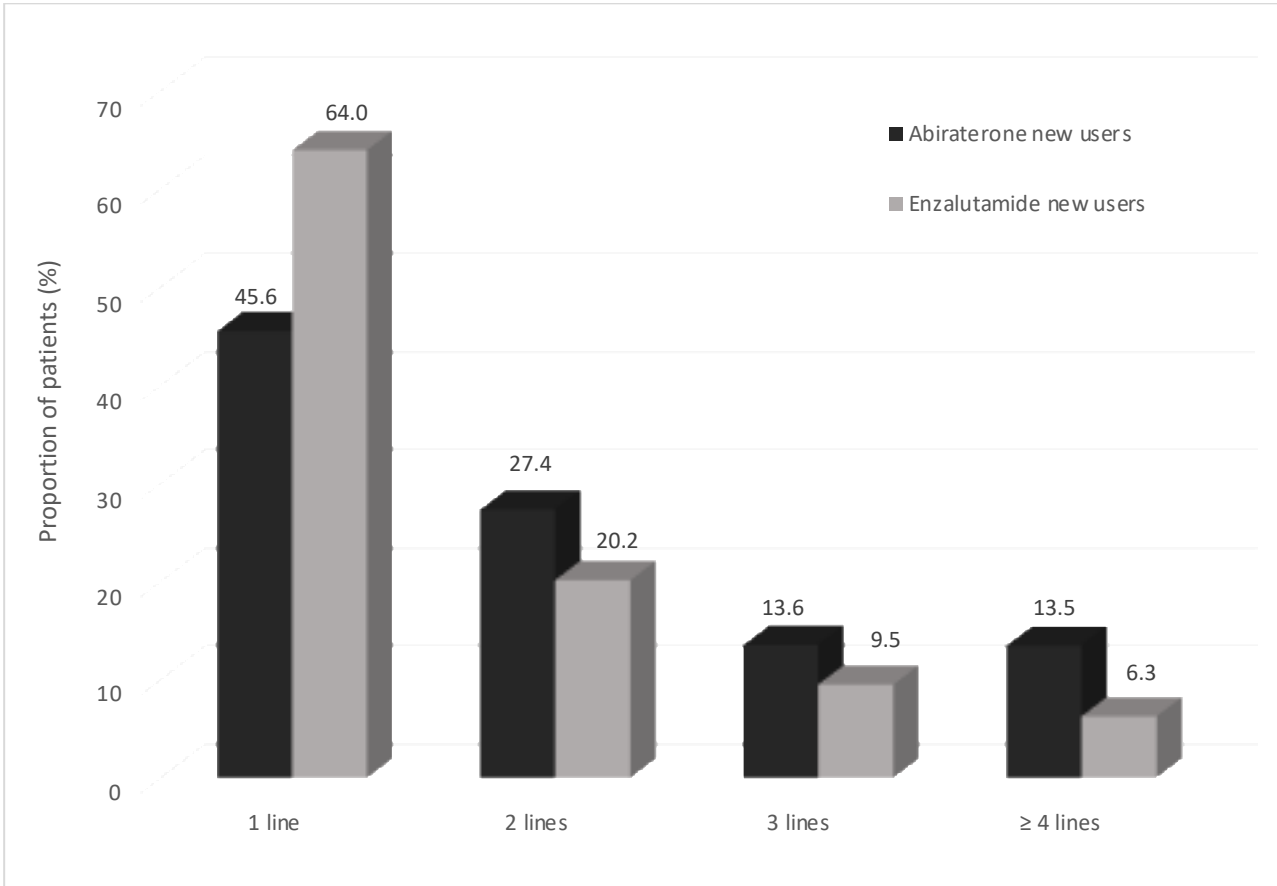
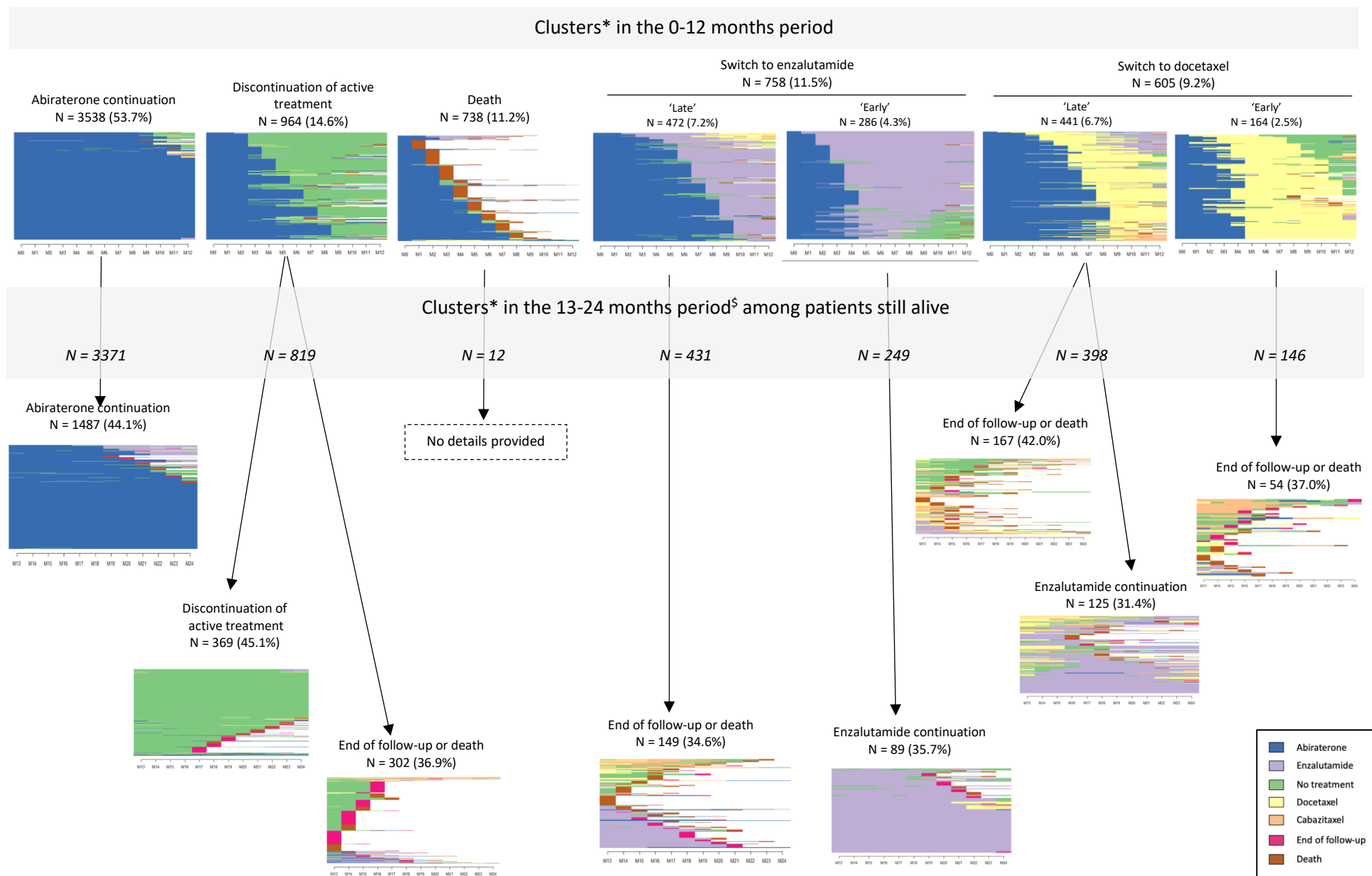
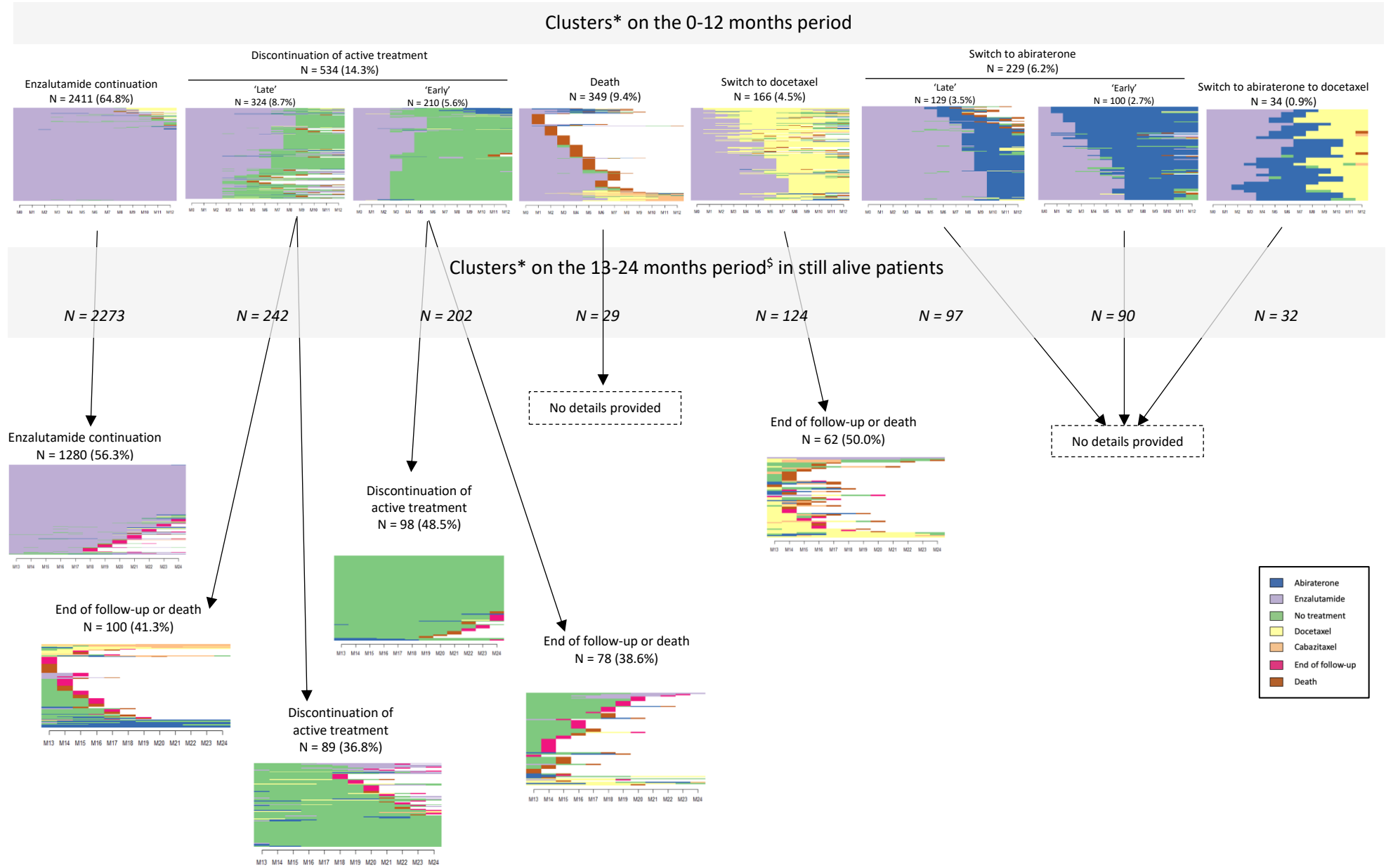


Figure 2.



*Although the ordinate of the graph is similar between clusters, each cluster involves a different number of patients.
\$ Only clusters involving > 30% of patients are presented for ease of reading.

Figure 3.



*Although the ordinate of the graph is similar between clusters, each cluster involves a different number of patients.
\$ Only clusters involving > 30% of patients are presented for ease of reading.

Table 1. Characteristics of 0-12 months clusters among ABI new users.

Cluster description	Only ABI	Discontinuation of active treatment	Death	'Late' Switch ABI to ENZ	'Early' switch ABI to ENZ	'Late' switch to docetaxel	'Early' switch to docetaxel
N (%)	3538 (53.7)	964 (14.6)	738 (11.2)	472 (7.2)	268 (4.1)	441 (6.7)	164 (2.5)
Age, mean ± SD (years)	76.3 ± 8.7	78.2 ± 10.3	82.2 ± 7.0	78.4 ± 8.1	80.1 ± 7.3	73.3 ± 7.9	72.9 ± 7.8
Charlson score							
0	218 (6.2)	93 (9.6)	52 (7.0)	29 (6.1)	10 (3.7)	28 (6.3)	9 (5.5)
1	34 (1.0)	29 (3.0)	9 (1.2)	3 (0.6)	3 (1.1)	6 (1.4)	1 (0.6)
2	2699 (76.3)	661 (68.6)	472 (64.0)	362 (76.7)	198 (73.9)	350 (79.4)	127 (77.4)
≥ 3	587 (16.6)	181 (18.8)	205 (27.8)	78 (16.5)	57 (21.3)	57 (12.9)	27 (16.5)
ADT duration before ABI initiation, n (%)							
< 2 years	1207 (34.1)	379 (39.3)	375 (50.8)	187 (39.6)	111 (41.4)	231 (52.4)	87 (53.0)
2 - 3 years	611 (17.3)	143 (14.8)	113 (15.3)	85 (18.0)	46 (17.2)	63 (14.3)	28 (17.1)
> 3 years	1656 (46.8)	381 (39.5)	229 (31.0)	191 (40.5)	105 (39.2)	143 (32.4)	48 (29.3)
Unknown	64 (1.8)	61 (6.3)	21 (2.8)	9 (1.9)	6 (2.2)	4 (0.9)	1 (0.6)

ABI: abiraterone, ENZ: enzalutamide, Q1-Q3: 1st and 3rd quartile, SD: standard deviation.

Table 2. Characteristics of 0-12 months clusters among new ENZ users.

Cluster description	Only ENZ	'Late' discontinuation active of treatment	'Early' discontinuation of active treatment	Death	'Late' Switch ENZ to ABI	'Early' switch ENZ to ABI	Switch to docetaxel	Switch to ABI then docetaxel
N (%)	2411 (64.8)	324 (8.7)	210 (5.6)	349 (9.4)	129 (3.5)	100 (2.7)	166 (4.5)	34 (0.9)
Age, mean \pm SD (years)	77.5 \pm 8.8	81.1 \pm 8.3	81.6 \pm 10.2	82.8 \pm 7.7	80.9 \pm 8.2	79.2 \pm 7.8	74.3 \pm 8.1	77 \pm 7.6
Charlson score								
0	177 (7.3)	30 (9.3)	27 (12.9)	28 (8.0)	11 (8.5)	6 (6.0)	6 (3.6)	2 (5.9)
1	26 (1.1)	7 (2.2)	4 (1.9)	5 (1.4)	2 (1.6)	-	2 (1.2)	1 (2.9)
2	1768 (73.3)	217 (67.0)	127 (60.5)	212 (60.7)	88 (68.2)	67 (67.0)	125 (75.3)	22 (64.7)
≥ 3	440 (18.2)	70 (21.6)	52 (24.8)	104 (29.8)	28 (21.7)	27 (27.0)	33 (19.9)	9 (26.5)
ADT duration before ENZ initiation, n (%)								
< 2 years	909 (37.7)	124 (38.3)	84 (40.0)	181 (51.9)	71 (55.0)	38 (38.0)	95 (57.2)	14 (41.2)
2 - 3 years	420 (17.4)	50 (15.4)	32 (15.2)	33 (9.5)	16 (12.4)	17 (17.0)	31 (18.7)	6 (17.6)
> 3 years	1038 (43.1)	134 (41.4)	79 (37.6)	129 (37)	41 (31.8)	45 (45.0)	38 (22.9)	14 (41.2)
Not known	44 (1.8)	16 (4.9)	15 (7.1)	6 (1.7)	1 (0.8)	-	2 (1.2)	-

ABI: abiraterone, ENZ: enzalutamide, Q1-Q3: 1st and 3rd quartile, SD: standard deviation.